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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,506	02/26/2004	Darwin J. Prockop	57616-5001-03	4991

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
08/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,506	PROCKOP ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 22, 2007 that includes a response to the final office action dated February 22, 2007, has been entered. No claims were amended or newly added. Claims 55-77 are pending in the application and under current examination.

Claim Objections

Claim 70 stands objected to as being a substantial duplicate of claim 56. As Applicants' response has deferred the issue until claim 56 is deemed allowable, the objection is maintained.

Response to Claim Rejections - 35 USC § 112 - Lack of Enablement

Claims 55-77 stand rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for the claimed invention. The rejection set forth on pp. 2-7 of the office action dated February 22, 2007 is maintained for reasons of record.

Applicants traverse the rejection, the thrust of the Examiner's assertions appears to be that the specification does not enable the use of the claimed methods due to a lack of evidence regarding their human implementation, and if true, the Examiner is asserting that the claimed invention lacks an *in vivo* utility and a §101 rejection for lack of utility would also have been proper. Further citing *In re Brana* and PTO's position regarding human clinical testing in establishing utility. Applicants' arguments have been fully considered, but are not found persuasive.

As indicated in MPEP 2164.07, the requirement of 35 U.S.C. 112, first paragraph as to how to use the invention is different from the utility requirement of 35 U.S.C. 101. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard,

but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101. In the instant case, no rejection under 35 U.S.C. 101 is of record, as the examiner has determined that the claimed subject matter meets the requirements under 35 U.S.C. 101. Thus, Applicants' arguments are not on point. As previously indicated, the invention claimed by Applicants, broadly encompassing methods of administering systemically or intraperitoneally, a mixed population of culture expanded autologous, allogeneic or syngeneic bone marrow stromal cells wherein the cells differentiate into various cell types, thus generating, or repairing any type of blood vessel (including major veins and arteries) in a mammal, in a tissue specific manner or treating any disease that may be associated with a vascular disorder, was not considered either predictable or well-established either at the time of the instant invention or in post-filing literature. Furthermore, the absence of working examples or an actual reduction to practice in Applicants' disclosure were additional consideration in the analysis of *Wands* factors in establishing an enabled disclosure for the claimed methods of the invention.

Applicants argue that the Examiner has selectively reviewed only those sections of the cited references that discuss potential pitfalls of the technology, while completely ignoring the central findings of the references, which clearly show that the invention is feasible. Referring to Nagaya et al. as an example, wherein the authors demonstrate that intravenously administered MSCs were capable of engraftment in the myocardium and differentiated into cardiomyocytes and vascular endothelial cells, resulting in myogenesis and angiogenesis, supporting the therapeutic value of these transplanted cells for generating blood vessels *in vivo*.

Such is not found persuasive, because the issue is not the ability of MSCs to differentiate into cardiomyocytes and endothelial cells, but whether the administration of a mixed population of stromal cells can generate any type of blood vessel in appropriate sites in a controlled manner, or repair and treat any type of blood vessel in mammals suffering from numerous diseases, disorders or conditions, following their systemic or intraperitoneal administration, as instantly claimed. The instant specification teaches that the invention is "based upon the discovery that stromal cells introduced into patients by the bloodstream, develop into bone cartilage and lung". Additionally stating: "Similarly, it is believed that stromal cells will also develop into cells of the dermis, blood vessels, heart and kidneys, or throw off daughter cells that will do so." (page 8,

line 14-29). As indicated in the previous office actions: "it would require undue experimentation to demonstrate that systemic or intraperitoneal administration of stromal cells would result in the proper differentiation and generation or repair of blood vessels at the site where said blood vessels are required, and not at undesired sites, for the methods of the instant application", because systemic administration of MSCs would result in the dilution of said cells in the animal and would further introduce stem cells to undesired locations wherein subsequent differentiation of the cells into various different lineages could complicate, rather treat a disease state.

With respect to the post-filing art of Nagaya et al., the teachings of Nagaya's abstract were summarized in the first office action and not ignored, contrary to Applicants' contention. Further, Nagaya's caution that "the limitation of this study is that the cell population may be mixed, rather than limited to MSCs" is highly relevant in view of Applicants' disclosure, because the instant specification notes that donor cells from marrow are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32). Thus, the cultured stromal cells of the instant invention as demonstrated by the instant disclosure are a mixed population of cells. Further, regarding Nagaya's observations in neovascularization, Nagaya et al. teach that some of the transplanted MSCs were positive for an endothelial cell marker and participated in vessel formation, and that the plasticity of MSCs to transform into endothelial-like cells provides a rationale for their potential role in neovascularization (first and second column, p. H2675). It should be noted that a blood vessel is not comprised of only endothelial cells, but a variety of cells that include epithelial and smooth muscle cells and a contribution to neovascularization is not synonymous with generation of any type of blood vessel as instantly claimed. It is further clear that the post-filing teachings of Nagaya et al. point to the need for further experimentation. As stated in MPEP 2164.05(a), the specification must be enabling as of the filing date. A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling. If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993).

In addressing the post-filing art of Zisch, Applicants reiterate that EPCs (endothelial progenitor cells) are not equivalent to the currently cited bone marrow stromal cells and that it is inappropriate for the Examiner to rely on this reference. Such is not persuasive because Zisch et al. describe the application of autologous endothelial stem/progenitor cells (EPCs) derived from bone marrow, for incorporation into sites of new vessel growth for the improvement of regional blood flow (Abstract). Moreover, the teachings of Zisch et al. were cited to demonstrate the plasticity of the stem cells can result in the cells developing into a number of different cell types, which is important in light of the systemic and intraperitoneal routes of administration of the instant claims, wherein administered MSCs could be transplanted at numerous sites in a mammal, causing potential undesired differentiation that would likely alter the physiological state of the mammal by providing paracrine growth factor/cytokine signals. These potential pitfalls are equally applicable to MSCs and EPCs, and are not based on complete conjecture, as alleged by Applicants, especially in view of the instant specification's disclosure that the MSCs introduced into patients by the bloodstream develop into bone cartilage, dermis, heart, kidneys and blood vessels. Further, as acknowledged by Applicants, the bone marrow derived stromal cells can differentiate into endothelial cells, as do endothelial stem/progenitor cells. The instant claims have not been rejected on the grounds of anticipation or obviousness, thus Applicants' arguments that Zisch et al. provide no suggestion that one should use BMSCs to create blood vessels is irrelevant.

Separately, Applicants argue that Zisch et al.'s statement is taken out of context and the full statement reads: "The interaction between the host environment and EPCs has not been well established...the surprising plasticity of primary EPCs to change fate into cardiomyocyte or mesenchymal phenotypes warrants further investigation so that their potential for exploitation in cardiovascular tissue engineering applications can be further appreciated.". It is clear therefore that while EPCs hold therapeutic potential, such potential warrants further investigation, even in post-filing art.

With respect to Dzau et al., Applicants assert that the reference is also directed to EPCs. In response, Applicants are directed to the foregoing commentary regarding EPCs. Applicants further argue that this reference also has been taken out of context by the Examiner and viewed only in a negative light, while the positive potential of the EPCs is ignored. In particular, the

Examiner has cited a paragraph from the section entitled "Potential Problems with Therapeutic Use of EPCs" regarding the impaired function of EPCs in certain populations and the importance of purity and developmental state of the cells. Applicants note that the impaired function of EPCs in certain patient populations (e.g., diabetic patients) does not preclude enablement of the invention. In other words, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, and that impairment of the EPCs in these patients would apply more particularly to autologous transplantation and not allogeneic transplantation.

Such is not found persuasive, because no enabled scope for the method of the instant invention has been indicated for either autologous or allogeneic BMSCs in generating blood vessels following their systemic and intraperitoneal administration. Further, the lack of enablement of the claimed methods is based on the totality of the art of record. That Dzau et al. highlight potential pitfalls with therapeutic use of autologous EPCs does not provide an enablement for the instantly claimed methods. It should additionally be noted that addressing potential pitfalls of EPCs in therapeutics is not equivalent to quotation out of context. The problems highlighted by Dzau et al. were addressed in the previous rejections because they are relevant to the issues of enablement.

Regarding the observations of Yoon et al., Applicants argue that only injection of total bone marrow cells led to calcification of the heart, and no echogenic areas were observed in rats receiving bone marrow stem cells or PBS. In response, it should be noted that calcification was observed in total bone marrow stem cells and not in BMSCs clonally selected as single cells that had undergone many population doublings (see first column, p. 3155). Yoon et al. state that the stroma is a heterogeneous mixture of cells including mesenchymal stem cells, multipotent adult progenitor cells, adipocytes, reticulocytes, endothelial cells, fibroblastic cells and osteoblasts and that any BM-derived stem cells could be considered as candidates for the induction of local calcification (second column, p. 3156). The instant claims are drawn to bone marrow stromal cells that the instant specification has noted to be a mixed population of donor cells that are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32).

Applicants have again failed to address issues regarding the use of MSCs in any treatment method, involving non-specific delivery of MSCs to a particular target site, and the potential for detrimental neovascularization at physiological locations where such vascularization is not required, or the functional impairment of the cells in patients with cardiovascular diseases (relevant to autologous transplantation), and the importance of the purity and developmental stage of the cells used for transplantation. As previously stated, exogenous mobilization of bone marrow with hematopoietic growth factors and other endothelial growth factors may recruit progenitor cells to sites of occult neoplasia, leading to vascularization of dormant tumors. In addition, mobilization could potentially accelerate progression of atherosclerotic plaque by recruiting inflammatory and vascular smooth muscle cell progenitor cells into the plaque, contributing to neointima hyperplasia and transplant arteriopathy, as well as contribution to allograft vasculopathy by promoting neovascularization of the plaque.

Thus, contrary to Applicants' assertions, the nature of the invention is not reasonably predictable given the lack of guidance in the specification, for the generation, repair or treatment of conditions requiring neovascularization to generate a blood vessel in a mammal and treat any vascular disease, following systemic or intraperitoneal administration of unpurified culture expanded bone marrow MSCs. It would require further and undue experimentation for a person of ordinary skill in the art to demonstrate the targeted delivery of MSCs to a desired site and the generation of a blood vessel from culture expanded stromal cells and the prevention of inappropriate neovascularization or unwanted angiogenesis, to make and use the claimed invention.

Therefore the rejection of claims 55-77 is maintained for reasons of record and the discussion set forth above.

Response to Obviousness Type Double Patenting

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-70 of copending Application No. 10/423,232. The rejection set forth on pp. 7-8 of the previous office action dated February 22, 2007 is maintained for claims 55-77 for reasons of record.

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-28 of copending Application No. 10/844,235. The rejection set forth on pp. 7-8 of the previous office action dated February 22, 2007 is maintained for claims 55-77 for reasons of record.

Applicants traverse the rejections, arguing that neither of these references teach or suggest in the claims a method for generating a blood vessel in a mammal, as the '232 claims are directed to a process of generating heart tissue and the '235 claims are directed to a method of treating a mammal having undergone marrow ablation. Applicants' arguments have been fully considered, but are not found persuasive.

As previously indicated, claims reading on heart tissue encompass the vasculature of the heart tissue, hence, the claims of copending Application No. 10/423,232 anticipate and fall entirely within the scope of the rejected claims of the instant application. The claims of copending Application No. 10/844,235 also overlap in scope, as both sets of claims recite a process comprising administering allogeneic bone marrow stromal cells to a mammal and entail the same method steps for the methods for generating, regenerating or repairing blood vessels.

Applicants state that a submission of a terminal disclaimer will be considered once the claims are determined to be allowable. However, in the absence of a terminal disclaimer the rejection of the claims is maintained.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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